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International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification 6 :</b> <b>A61K 38/00, 39/00, 39/44, 39/395, 51/00, C07K 2/00, 4/00, G01N 33/53, 33/543, 33/566</b>		<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/64037</b> <b>(43) International Publication Date:</b> 16 December 1999 (16.12.99)
<b>(21) International Application Number:</b> PCT/US99/12620 <b>(22) International Filing Date:</b> 8 June 1999 (08.06.99)		<b>(74) Agents:</b> SWISS, Gerald, F. et al.; Burns, Doane, Swecker & Mathis, L.L.P., P.O. Box 1404, Alexandria, VA 22313-1404 (US).	
<b>(30) Priority Data:</b> 60/088,448 8 June 1998 (08.06.98) US 60/093,072 16 July 1998 (16.07.98) US		<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
<b>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications</b> US 60/088,448 (CON) Filed on 8 June 1998 (08.06.98) US 60/093,072 (CON) Filed on 16 July 1998 (16.07.98)		<b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
<b>(71) Applicant (for all designated States except US):</b> ADVANCED MEDICINE, INC. [US/US]; 280 Utah Avenue, South San Francisco, CA 94080 (US).			
<b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> GRIFFIN, John, H. [US/US]; 56 Walnut Avenue, Atherton, CA 94027 (US). JUDICE, J., Kevin [US/US]; 146 1st Street, Montara, CA 94037 (US).			
<b>(54) Title:</b> NOVEL THERAPEUTIC AGENTS THAT MODULATE ENZYMATIC PROCESSES			
<b>(57) Abstract</b> Novel multi-binding compounds are disclosed that modulate enzymatic processes. The compounds of the invention comprise from 2-10 ligands covalently connected, each of said ligands being capable of binding to an enzyme, enzyme substrate or enzyme cofactor thereby modulating the biological processes/functions thereof.			

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NOVEL THERAPEUTIC AGENTS THAT MODULATE ENZYMATIC PROCESSES  
NOUVEAUX AGENTS THERAPEUTIQUES MODULANT LES PROCESSUS ENZYMATIQUES

Patent Applicant/Assignee:

ADVANCED MEDICINE INC,  
GRIFFIN John H,  
JUDICE J Kevin,

Inventor(s):

GRIFFIN John H,  
JUDICE J Kevin,

Patent and Priority Information (Country, Number, Date):

Patent: WO 9964037 A1 19991216  
Application: WO 99US12620 19990608 (PCT/WO US9912620)  
Priority Application: US 9888448 19980608; US 9893072 19980716

Designated States: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE  
ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT  
LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT  
UA UG US US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ UG ZW AM AZ BY KG KZ  
MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ  
CF CG CI CM GA GN GW ML MR NE SN TD TG

Publication Language: English

Fulltext Word Count: 58767

English Abstract

Novel multi-binding compounds are disclosed that modulate enzymatic processes. The compounds of the invention comprise from 2-10 ligands covalently connected, each of said ligands being capable of binding to an enzyme, enzyme substrate or enzyme cofactor thereby modulating the biological processes/functions thereof.

French Abstract

L'invention porte sur de nouveaux composes multi-liants modulant les processus enzymatiques. Lesdits composes comportent de 2-10 ligands unis par covalence dont chacun peut se fixer a une enzyme, a un substrat d'enzyme ou a un cofacteur d'enzyme et modifier par la leurs processus et fonctions biologiques.

Fulltext Availability:

Detailed Description  
Claims

Detailed Description

... effects.

Other examples of diseases in which enzymes are involved include infectious diseases caused by **bacteria**, protozoa or fungi, viral diseases such as AIDS (e.g., reverse transcriptase or protease enzymes... rasagiline, 1370U, L-650477, indeloxazine, Alzheimer's disease moclobemide, brofaromine, EXP-631 Neurodegenerative disease

Dementia

**Dihydrofolate reductase** Cancer Methotrexate., edatexate. piritrexim, LY LY-316373, (1 1.3) Psoriasis 1954U89, E-34335, AG...tumor

Uterine cervix tumor

Bladder tumor

Urinary tract tumor

Renal tumor

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Ribosomal protein biosynthesis **Bacterial** infection Chloramphenicol, erythromycin, clarithromycin, azithromycin, (50S ribosomal subunit) **Pneumocystis carinii** infection dirithromycin, flurithromycin clindamycin, lincomycin **bacteria** ] Tetracycline, chlortetracycline, oxytetracycline, demeclocycline, (Aminoacyl tRNA site on 30S

methacycline, doxycycline, minocycline, CL-331002, ribosomal...

...CL-331928, CL-344667, CL-329998, PAM-MINQ

(2 2.12)

Ribosomal protein biosynthesis Anti- **bacterial** Streptomycin, gentamicin, tobramycin, amikacin, netilmicin, (30S subunit) kanamycin, neomycin, spectinomycin, dactimycin, paromomycin,

(2 2.12) trospectornycin

Ribosomal protein biosynthesis Anti- **bacterial** Fusidic acid, purpuromycin

(soluble protein factors)

(2 2.12)

Glucan synthase Fungal infection LY-303366...

...H)-one,

COP-5241 1. RG-8803, BP SU-6668

Beta subunit of DNA-dependant **Bacterial** infection Rifampin, rifabutin, rifalazil, T9, SPA-S-565

RNA polymerase

(2 7.6)

DNA polymerase...A-502 I 1. SPV-30, VF-1 618, TNK-651

19

D,D-transpeptidases **Bacterial** infection Beta-lactams

(PBP 2a.- 2b) Penicillin G, penicillin V, methicillin, nafcillin.

oxacillin.

cloxacillin, dicloxacillin...

...meziocillin, piperacillin,

(PBP 1a) cephalothin, cefazolin, cephalexin, cefadroxil, cefamandole, cefoxitin, cefaclor, cefuroxime, loracarbefcefonicid,

D,D- **Carboxypeptidase** cefotetan, ceforanide, cefotaxime, cefpodoxime proxetil,

(PBP 3-7) ceftizoxime, ceftriaxone, cefopcravzone, ceftazidime, cefepime,

(3 16...CH-263, marimastat analogs

(3 24) Inflammatory bowel disease

Rheumatoid arthritis

Ulcerative colitis

Beta-Lactamase **Bacterial** infections Clavulanic acid, sulbactam.

tazobactam. Ro 0480, HM-3030, (3 2.6) GD40, Ro48-8724...

...186195, DWC-751, 2085-P, CP

72436, BK-218, BRL42715, SB-223328, Ro 1317

Undecaprenyldiphosphatase **Bacterial** infections Bacitracin

(3 1.27)

H+/K<sup>+</sup> ATPase Peptic ulcer Omeprazole, leminoprazole, rabeprazole, esomeprazole, SKF...

...34655, Ro 5364, T-776, nicotinamide

Gastrointestinal disease derivatives, pantoprazole, lansoprazole,

SKF-96067, SPI-1447,

**Bacterial** infection AD-9161, YJA-20379, A-28200, SKF-96356, YM-020,

Fungal infection baflornycin A derivatives, atractylone, saviprazole,

OPC-22575

Parasite infection

Isomerase Enzymes

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DNA gyrase **Bacterial** infections Nalidixic acid, norfloxacin, ofloxacin, ciprofloxacin, cinoxacin, (5 1.3)- Fungal infections sparfloxacin,

lomefloxacin, fleroxacin...NSAIDs) including aspirin, indomethacin, ibuprofen, and naproxen. A fourth example of an oxidoreductase enzyme is

**dihydrofolate reductase** (DHFR), which catalyzes the conversion of dihydrofolate polyglutamate to tetrahydrofolate polyglutamate ...is

selectively inhibited by the antibacterial agent rifampin. In a third example, protein biosynthesis in **bacterial** cells is selectively inhibited by a variety of antibiotics (including gentamicin and other aminoglycosides, tetracycline...).

...transglycosylase responsible for the glycosyl transferase reaction which incorporates lipid intermediate 11 into the growing **bacterial** cell wall. Vancomycin acts via a substrate sequestration mechanism; i.e., it binds to and...

...the action of a series of penicillin binding proteins (PBPs), most notably multifunctional, membrane-bound **transpeptidase** enzymes that are responsible for cross-linking of the **bacterial** cell wall.

3. Hydrolase enzymes mediate particular subsets of transfer reactions in which moieties are...

...which is then available for reuse as the lipid carrier for intermediates 27

involved in **bacterial** cell wall biosynthesis. The topical antibacterial agent bacitracin inhibits the diphosphatase process by sequestering the ...dazoxiben and pirmagrel. A third example of an isomerase is alanine racernase, a soluble, monomeric **bacterial** enzyme that produces D-alanine for incorporation into the cell wall. A fourth example of...

...agents, in particular the quinolones, which inhibit the alpha2beta2 tetrameric topoisomerase II (DNA gyrase) in, **bacterial** cells, and also etoposide, and teniposide, which inhibit the mammalian topoisomerase 11 enzyme.

6. Ligase...

...mediates the ATP-dependent condensation of two D-alanine subunits as an early step in **bacterial** cell wall biosynthesis.

Nearly all known enzymes are proteins. As is true for all proteins... disease states include, but are not limited to, treatment of a mammal afflicted with pathogenic **bacteria**, in particular staphylococci (methicillin sensitive and ...to inhibit gastric acid secretion as described in U.S.

Patent 4,255,43 1.

#### **Dihydrofolate reductase**

Anti-leukemia activity is monitored using L 1 21 0 leukemia according to the method...and Carboxyl Groups

Bacitracin is an antibacterial antibiotic that inhibits an enzymatic process involved in **bacterial** cell wall biosynthesis. Bacitracin is a widely utilized animal growth promoter and an important component...

...antibacterial ointments. Bacitracin is effective against a subset of both Gram-positive and Gram-negative **bacteria** in vitro, and it has recently shown promising activity against vancomycin-resistant Enterococcus faecium in...isocarboxazid trantivcypromine. selegifine (1 3.6) Depression

Dihydrofolate redUCt2se Anti-parasite Chloroguanide. pyrimeLhamme (microbial) Anti- **bacterial** Trimethoprim

(1 1.3)

Dihydrofolate reductase Monomer Anti-cancer lvlethotrexate

(1 1.3) Psoriasis

Trypanathione **Dihydrofolate reductase** In vitro Synthetic analogues of trimethoprim were tested

%4 inhibitory effects on protozoan and mammalian

in **dihydrofolate reductase** using standard analytical methods

Fn

CD

6-Phosphogluconate In vitro Inhibitors of enzyme activity tested...that bind

M 80

tD (PBP 1-6) PBPs and block cell wall synthesis by **bacteria**, were studied

r

M

Transglycosylase In vitro The inhibition of cell wass synthesis was  
studiec...

...of dihydropteroate synthase by  
sulfanilanifides with 3',5'-halogen substitutions

Fn evaluated

CD

D,D- **carboxypeptidase** in vitro Inhibition of enzyme, expressed by  
Ochrobactru

(PPB 3-7) anthropi studied

Table 2...racemase In vitro Inactivators of alanine racemase were  
evaluated

cultures of Gram positive and negative **bacteria**

M

C

W

U)

I Prostacyclin synthase In vitro The effect of enzyme inhibition on...

...effects of inhibitors of cylcas

were tested

DNA gyrases In vitro Effect of inhibitors, of **bacterial** gyrases, was  
studied in vitro using time-kill assays 39(12):282

Topoisomerase 11 In...

Claim

... the enzyme is acrosin, the figand cannot be a benzamidine;  
when the enzyme is a **bacterial** transglycosylase, the figand cannot be a  
glycopeptide; when the enzyme is **bacterial** DNA gyrase, the figand  
cannot be a quinolone;

when the enzyme is thrombin, the ligand...claim 12, wherein the method is  
chosen from treatment of a mammal afflicted with pathogenic **bacteria**,  
psoriasis, multiple sclerosis, rheumatoid arthritis, insulinindependent  
diabetes, breast cancer and prostate cancer, disease states related...

?